## REMARKS

Claims 74, 75-78, 90, 93 and 94 are pending and under consideration.

### Regarding the Oath/Declaration

Applicants will submit a new Declaration under separate cover.

### Regarding 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 74, 76, 78, 90, 93 and 94 under 35 U.S.C § 112, second paragraph, for allegedly failing to comply with written description requirement.

*Enzo Biochem v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) ("Enzo Biochem II"), stated that "the written description requirement would be met for all of the claims [of the patent at issue] if the functional characteristic of [the claimed invention was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." In *Invitrogen v. Clontech*, the Federal Circuit held that the disclosure of a single genetically-engineered functional variant of a known protein was sufficient to provide adequate written description to support a claim encompassing essentially any engineered variant of the protein sharing the modified function. 429 F.3d 1052 (Fed. Cir 2005)

Claim 74 recites that the method for diagnosing colon, breast or prostate cancer in a patient includes comparing a level of VLDLR mRNA having a nucleotide sequence at least 95% identical to the sequence of SEQ ID NO:43 in a patient sample comprising colon, breast or prostate tissue to the level of the VLDLR mRNA in a normal control; and diagnosing colon, breast or prostate cancer in the patient based on an increase of at least 50% from the level of the VLDLR mRNA in the patient sample relative to the level in the normal control. Claim 90 recites contacting a polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleotide sequence of SEQ ID NO:43 with nucleic acids of a patient colon, breast or prostate sample under binding conditions suitable to form a duplex, wherein hybridization is performed at 50°C to 60°C in 5 X SSC (9 mM saline /0.9 mM sodium citrate); and (b) comparing the amount of the duplex formed to the amount of duplex formed when the

polynucleotide is contacted with nucleic acids of a non-cancerous colon, breast or prostate control, and c) diagnosing colon, breast or prostate cancer based on an increase of at least 50% of the amount of duplex formed upon contacting the polynucleotide with the nucleic acids of the patient sample compared to the amount of duplex formed upon contacting the polynucleotide and the nucleic acids of the non-cancerous control.

Applicants submit that independent claims 74 and 90 have written description sufficient to satisfy the MPEP, the Written Description Guidelines, and the relevant case law. An adequate description is one that describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Possession may be shown in a variety of ways. For example, possession can be found where an Applicant presents drawings of the claimed invention (as in Vas-Cath) or structural chemical formulas. An Applicant may also describe distinguishing identifying characteristics. Pfaff v. Wells Elecs., Inc., 525 U.S. 55 (1998); Amgen, Inc. v. Chugai Pharm., 927 F.2d 1200 (Fed. Cir. 1991) (one may define a compound by "whatever characteristics sufficiently distinguish it").

The specification provides sufficient written description for the pending claims as evidenced by the U.S. Patent and Trademark Office's own guidelines on the subject: Written Description Training Materials (Revision 1 March 25, 2008), available at http://www.uspto.gov/web/menu/written.pdf ("Guidelines"). Example 11 of the Guidelines illustrates a hypothetical situation that is analogous to the present case. Example 11 provides an analysis of a claim that recites "an isolated nucleic acid that encodes a polypeptide with at least 85% amino acid sequence identity to SEQ ID NO: 2."

Example 11 then provides the following guidance to examiners:

> Claim 1 encompasses nucleic acids that encode the polypeptide of SEQ ID NO: 2, as well as those that encode any polypeptide having 85% structural identity to SEQ ID NO: 2. However, the specification discloses only a single species that encodes SEQ ID NO: 2; i.e., SEQ ID NO: 1. There are no other drawings or structural formulas disclosed that encode either SEQ ID NO: 2 or a sequence with 85% identity to SEQ ID NO: 2. The recitation of a polypeptide with at least 85% identity represents a partial structure, that is, at least 85% percent of the amino acids in the polypeptide will match those in SEQ ID NO: 2, and up to 15% of

them may vary from those in SEQ ID NO: 2. However, there is no teaching regarding which 15% of the amino acids may vary from SEQ ID NO:2. Consequently, there is also no information given about which nucleotides will vary from SEQ ID NO: 1 in the claimed genus of nucleic acids.

There is no functional limitation on the nucleic acids of claim 1 other than that they encode the polypeptide of SEQ ID NO: 2 or any polypeptide having 85% structural identity to SEQ ID NO: 2. The genetic code and its redundancies were known in the art before the application was filed. The disclosure of SEQ ID NO: 2 combined with the pre-existing knowledge in the art regarding the genetic code and its redundancies would have put one in possession of the ge nus of nucleic acids that encode SEQ ID NO: 2. With the aid of a computer, one of skill in the art could have identified all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2. Thus, one of ordinary skill in the art would conclude that the applicant was in possession of the claimed genus at the time the application was filed.

The nucleotide of claims 74, 76, 78, 90, 93 and 94 must have at least 95% sequence identity to SEQ ID NO: 43. Applying the principles of the analysis set forth in the Guidelines' Example 11, Applicants respectfully submit that the disclosure of SEQ ID NO: 43 combined with the pre-existing knowledge in the art regarding the genetic code and its redundancies would have put one in possession of the genus of claimed nucleic acids. With the aid of a computer, one of skill in the art could have identified all of the nucleic acids that have at least 95% sequence identity with SEQ ID NO: 43. mRNA having a nucleotide sequence at least 95% identical to the sequence of SEQ ID NO:43. Thus, one of ordinary skill in the art would conclude that the applicant was in possession of the claimed genus at the time the application was filed. Contrary to the Office's suggestion, there is no functional requirement for SEQ ID NO: 43 and it is not analogous to the tyrosine kinase activity that was a requirement in claim 3 of the Written Materials. A 50% increase is not at all a requirement, if it was the methods would be inoperable for diagnosing cancer based on a 50 % increase. The Written Description Guidelines state regarding Example 6, Claim 3 that "the disclosure of SEQ ID NO: 1 combined with the knowledge in the art regarding hybridization would put one in possession of the genus of nucleic acids that would hybridize under stringent conditions to SEQ ID NO: 1." The Guidelines go on to explain that the lack of written description is due to the inability of the skilled artisan to further determine which variants would also encode a polypeptide that binds to NDG receptor and stimulates tyrosine kinase activity. There is no such functional requirement in the rejected claims. Applicants respectfully request removal of the rejection of claims 74, 76, 78, 90, 93 and

94 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, had possession of the claimed invention at the time the application was filed.

**Regarding 35 U.S.C. § 112, First Paragraph (Enablement)**

Applicants respectfully traverse the rejection of claims 74, 76, 78, 90, 93 and 94 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Applicant respectfully maintains that the specification enables the full scope of the claimed invention for the reasons that follow.

In *Amgen, Inc. v. Hoechst Marion Roussel, Inc*, 232 F.3d 905 (Fed.Cir. 2000), the Federal Circuit clarified the enablement requirement:

> The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation."

Id. (citing *Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991))

In *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

*Id.* (Emphasis added) (citing *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d at 1564, 37 U.S.P.Q.2d at 1623); see also *In re Wands*, 858 F.2d at 736-40, 8 U.S.P.Q.2d at 1403-07.

It is respectfully submitted that the skilled artisan, armed with the teachings of the specification would have been able to practice the claimed methods without undue experimentation by confirming that the variants are overexpressed in breast cancer cells via

routine methods not requiring undue experimentation. Applicants respectfully request removal of the rejection of claims 74, 76, 78, 90, 93 and 94 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

**Regarding 35 U.S.C. § 102**

Applicants respectfully traverse the rejection of claims 74, 76-78, 93 and 94 under 35 U.S.C. § 102(b), as allegedly anticipated by Martensen et al., Eur. *J.Biochem* 248:583-591 (1997).

The Office alleges that Martensen et al. disclose "method steps of determining breast cancer comprising comparing the levels of expression of gene product in breast cell lines and carcinoma tissue samples to the normal cells or tissues." The Office Action cites Figures 1 and 5 for this alleged disclosure. It is respectfully pointed out that the samples in Figures 1 and 5 have already been determined to be breast carcinomas, such that there is no disclosure of an active step of diagnosing cancer based on an increase in the expression product. The Office further alleges that "Martensen et al. compare the gene expression pattern from the cell line isolated from breast cancer tissues to the normal cells and display the expression levels (figure 5) that is more than 50%, 100% or more increased." It is respectfully pointed out that the Martensen et al. reference does not disclose that cancer can be diagnosed based on an increase of at least 50% between the level of the expression product in the individual's tissue sample and a control sample. The tissue samples in Martensen et al. are all preselected because they are breast carcinomas. There is no disclosure of an active step of diagnosing cancer based on a 50% increase in the expression product.

"[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008).

"The prior art reference must clearly and unequivocally disclose the claimed invention or direct those skilled in the art to the invention without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.", *Net MoneyIN, Inc., supra,* quoting *In re Arkley*, 455 F.2d 586 (CCPA 1972).

The Examiner has not shown where Martensen et al. teaches each and every step of the claimed methods. Martensen et al. does not teach or suggest methods of diagnosing breast cancer including an active step of diagnosing cancer based on a 50% increase in the expression product of SEQ ID NO: 243. Accordingly, Martensen et al. does not clearly and unequivocally disclose the claimed invention including all of the limitations arranged or combined in the same way as recited in the rejected claims. Applicants respectfully request removal of the rejection of claims 68-69, 94-107 and 110 under 35 U.S.C. § 102(b) as allegedly being anticipated by Martensen et al., *Eur. J.Biochem* 248:583-591 (1997).

**Regarding 35 U.S.C. § 103**

The Office rejected claim 90 under 35 U.S.C. §103 as allegedly being unpatentable over Martensen et al. in view of Hopkins et al. and Fodor et al. (U.S. Patent No. 5,872,928). Applicants respectfully disagree.

As described above, Martensen et al. disclose that breast carcinomas expressed predominantly a VLDLR variant lacking exon 16 as determined by RT-PCR. Hopkins et al. discloses that SEQ ID NO:5 is down-regulated two-fold or more in activated T cells. Fodor et al. discloses methods for analyzing nucleic acids. The combination of cited references does not disclose that cancer can be diagnosed based on an increase of at least 50% in the amount of duplex formed as recited in claim 90. Neither Hopkins et al., nor Fodor et al. address any of the deficiencies of the primary reference by Martensen et al. Accordingly, the combination of cited references does not render claim 90 obvious and the Office is requested to withdraw the rejection under 35 U.S.C. §103.

## CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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